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Title: Comparison of Telavancin and Vancomycin Antibiotic Lock Solutions in the Eradication of Biofilm-Producing Staphylococci and Enterococci from Central Venous Catheters

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1 **ABSTRACT**

2 PURPOSE: Antibiotic lock solutions (ALS) are used for management of catheter-related
3 bloodstream infections. We compared activity of vancomycin and telavancin against
4 biofilm-forming *Staphylococcus epidermidis*, *Enterococcus faecalis*, and
5 *Staphylococcus aureus*.

6 METHODS: An established *in vitro* central venous catheter antibiotic lock model was
7 used to evaluate: vancomycin (5 mg/mL) and telavancin (5 mg/mL), with and without
8 preservative-containing heparin sodium (benzyl alcohol 0.45%) 2500 units/mL; and
9 heparin and normal saline. ALS were introduced after 24h bacterial growth in catheters
10 incubated at 35°C. After 72h exposure to lock solution, catheters were drained, flushed,
11 and cut into segments for CFU/mL quantification.

12 RESULTS: Against *S. epidermidis*, vancomycin and telavancin (with and without
13 heparin) demonstrated similar activity. Against *E. faecalis*, vancomycin alone (no
14 heparin) was more active than telavancin alone ($p < 0.01$). Against *S. aureus*,
15 vancomycin plus heparin demonstrated activity similar to vancomycin alone. Both
16 demonstrated greater activity than telavancin ($p < 0.02$). When heparin was added to the
17 vancomycin lock, activity against *S. epidermidis* and *E. faecalis* was reduced ($p < 0.01$).
18 Telavancin activity was not significantly changed with addition of heparin.

19 CONCLUSION: Both telavancin and vancomycin significantly reduced biofilm burden
20 against biofilm-forming *S. epidermidis*, *E. faecalis*, and *S. aureus*, but were unable to
21 completely eradicate these bacteria in the *in vitro* catheter model.

22 INTRODUCTION

23 Staphylococcal and enterococcal infections are a major problem in hospital
24 settings, especially among patients with indwelling devices.¹ These infections are often
25 caused by biofilm-producing strains which are difficult to eradicate and which may
26 progress to bacteremia. Vancomycin therapy is one of the recommendations in the
27 Infectious Diseases Society of America catheter-related infection management
28 guidelines when systemic antibiotics are used in combination with antibiotic lock
29 solutions (ALS) to treat catheter-related bacteremia while attempting to retain the
30 catheter.²

31 Telavancin is a lipoglycopeptide antibiotic with a core chemical structure similar
32 to the glycopeptide vancomycin. Unlike vancomycin, telavancin possesses a second
33 mechanism of action that causes a rapid depolarization and loss of the functional
34 integrity of the bacterial membrane.^{3, 4} Clinical data support the use of telavancin in the
35 treatment of complicated skin and soft-tissue infections and nosocomial pneumonia⁵⁻⁸,
36 while animal model data suggest efficacy in the treatment of bacteremia, endocarditis,
37 osteomyelitis, and meningitis caused by gram-positive pathogens.⁹⁻¹³ Of great interest is
38 the activity of telavancin against biofilm-producing staphylococci and enterococci.^{6, 14}
39 We previously described the activity of daptomycin and vancomycin on formed biofilms
40 in an in vitro central venous catheter model.¹⁵

41 We have used a validated catheter modeling system to assess the activity of
42 telavancin or vancomycin alone or in combination with the anticoagulant heparin
43 (containing benzyl alcohol preservative) in the eradication of biofilm-forming
44 staphylococci and enterococci. This model uses 72 hour lock times that are useful in
45 clinical settings, particularly in the management of hemodialysis catheter infections.^{16, 17}

46 **MATERIALS AND METHODS:**

47 **Bacterial strains.** Known biofilm-producing strains of *Staphylococcus epidermidis*
48 (ATCC 35984), methicillin-susceptible *Staphylococcus aureus* (MSSA, ATCC 35556),
49 and *Enterococcus faecalis* (ATCC 29212; vancomycin- susceptible) were evaluated. In
50 addition, biofilm-forming clinical isolates of *S. epidermidis* (L369D, from urine),
51 vancomycin-resistant *E. faecalis* (VRE, L2022, from tissue), methicillin-resistant *S.*
52 *aureus* (MRSA; L32 and L83, from blood), and MSSA (L2, from blood), were evaluated.
53 The biofilm forming ability of each strain, as determined by optical density
54 measurements, has been previously described.¹⁴ Minimum inhibitory concentrations of
55 vancomycin (1 to 2mg/L except the VRE strain at 256mg/L) and telavancin (0.03-0.25
56 mg/L) were also previously tested.¹⁴

57 **Lock solutions.** Vancomycin hydrochloride^a (5mg/mL final concentration) and
58 telavancin^b (5mg/mL final concentration) were obtained from commercial pharmacy
59 stock. Telavancin drug product (telavancin for injection, 250mg vial) also contains
60 mannitol (312.5mg) and hydroxypropylbetadex (2500mg) to increase solubility. Stock
61 solutions of each antibiotic were freshly prepared each day. Heparin sodium solution
62 (5000units/mL with 0.9% benzyl alcohol; Hospira, Lake Forest, IL) was obtained from
63 commercial pharmacy stock and diluted with normal saline (NS; without preservatives)
64 or antibiotic solution to a final concentration of 2500units/mL which contained 0.45%
65 benzyl alcohol. These lock solutions have demonstrated compatibility and stability up to
66 72h at 37°C.¹⁸

^a Hospira, Lake Forest IL, lot # 943903A, 12070DD

^b Astellas Pharma, Deerfield IL, lot# 2029222

67 **Medium.** Supplemented Tryptic soy broth (STSB, Difco, Becton Dickinson Co., Sparks,
68 MD) with 1% dextrose, 2% sodium chloride, 25 mg/L calcium chloride, and 12.5 mg/L
69 magnesium was used for all catheter models.^{15, 19} Colony counts were determined using
70 tryptic soy agar (TSA, Difco, Becton Dickinson Co., Sparks, MD).

71 **Device inoculation and treatment.** Two sets of catheters were processed. For all
72 catheters, a 0.5 McFarland standard of each test organism (noted above) was diluted in
73 STSB and added to the lumen of triple-lumen polyurethane central venous catheters
74 (Arrow-Howes CVC® 15703, Reading, PA).^{15, 19} Starting inocula were $\sim 10^6$ CFU/mL,
75 verified by colony count on TSA. After 24h biofilm development at 35°C, one set of
76 catheters was processed for CFU/mL to determine a baseline of biofilm formation. The
77 other catheters were drained and lock solution instilled. Under sterile conditions, each
78 drug was injected into each access port sufficient to fill the catheter lumen. Catheters
79 were then clamped at the distal end. This procedure was also repeated with separate
80 CVC containing anticoagulant (preservative-containing heparin sodium) or NS. Each
81 catheter was then incubated at 35°C for an additional 72h. Each organism was tested
82 against each agent at least in triplicate.

83 **Recovery of treated organisms.** Catheter fluid was removed and discarded following
84 incubation. A sterile needle was introduced into the open lumen and 1 mL of sterile NS
85 was flushed through each lumen and collected. To optimize yield of viable bacteria, the
86 flushed saline was sonicated at 60Hz for 1 minute, then vortexed for 15 seconds as
87 previously described.¹⁵ Additionally, 3 cm cut pieces of each catheter were sonicated
88 and vortexed in 3 mL of sterile NS. Sonication served to separate clusters of cells for
89 quantification, as well as removing biofilm from the catheter surface. Serial dilutions of

90 the flushed saline and saline used to sonicate and vortex the cut segments were plated
91 on TSA for colony count enumeration. The limit of detection for the flushed, sonicated,
92 and vortexed cultures from the lumen and the sonicated and vortexed saline of the
93 catheter segment is $2.0 \log_{10}$ CFU/mL.¹⁵

94 **Drug Stability.** Concentrations of vancomycin and telavancin with and without heparin
95 were evaluated before and after 72h incubation in CVC at 35°C. Vancomycin
96 concentrations were determined by a homogeneous particle-enhanced turbidmetric
97 immunoassay (PETIA; Architect, Multigent®; Abbott Diagnostics Abbott Park, IL, USA)
98 at the Providence Veteran Affairs Medical Center.²⁰ The vancomycin assay has a
99 detection range of 0.5 to 80.0 µg/mL, and an intra- and inter-day CV% of <2.0% and
100 <5.0%, respectively. Telavancin concentrations were determined by Theravance, Inc.
101 using liquid chromatography mass spectrometry.^{21, 22}

102 **Data analysis.** Each catheter was used to test one lock bacterial strain combination in
103 triplicate. The \log_{10} CFU/mL from the flushed saline and saline used to sonicate and
104 vortex the cut catheter segment were added together to give a total \log_{10} CFU/mL
105 result. This allowed for quantification of the total biofilm remaining in the catheter and
106 allowed for combining catheter lumens of different gauges. These triplicate total results
107 were subtracted from the baseline catheter (0h lock solution, $\sim 10^8$ CFU/mL, also in
108 triplicate) for each strain (n=9 per strain), to determine antimicrobial activity (reduction in
109 \log_{10} CFU/mL, or kill). Average activity and standard error of the mean were calculated
110 for each species and lock solution. Activity was compared between groups using one-
111 way ANOVA followed by Tukey's post-hoc test for multiple comparisons. All statistical

112 analyses were performed using SPSS statistical software (release 20; SPSS, Inc.
113 Chicago, IL.). A p value of < 0.05 indicates statistical significance.

114 RESULTS

115 **Antimicrobial activity in a catheter model.** Activity of tested lock solutions are shown
116 in **Figure 1a-c**. The activity of each lock solution was averaged for *S. epidermidis*, *E.*
117 *faecalis*, and *S. aureus*, as the results were similar for each species. The catheters
118 processed after 24h incubation with media and bacteria, with no lock solution, yielded
119 10^7 - 10^8 CFU/mL for each strain. This served as the baseline biofilm formation for
120 calculating activity of the lock solutions. Against *S. epidermidis*, all antibiotic lock
121 solutions were more active than normal saline ($p < 0.01$). Telavancin plus heparin
122 demonstrated the most activity, but was not significantly more active than telavancin
123 alone or vancomycin alone. The addition of heparin to vancomycin, however, reduced
124 activity compared to vancomycin alone (mean difference 0.79, 95%CI 0.15-1.42,
125 $p < 0.01$).

126 Against *E. faecalis*, telavancin demonstrated minimal activity. Vancomycin alone
127 was more active than the other lock solutions ($p < 0.01$). Vancomycin activity was
128 reduced by the addition of heparin (mean difference 2.89, 95%CI 2.42-3.36, $p < 0.01$).
129 Normal saline was more active than any heparin-containing lock solution or telavancin
130 alone ($p < 0.01$), suggesting that heparin reduces antimicrobial activity of the lock
131 solution.

132 Against *S. aureus*, antibiotic lock solutions demonstrated more activity than
133 heparin alone ($p < 0.02$), however telavancin and telavancin plus heparin were not
134 significantly more active than normal saline. Vancomycin plus heparin demonstrated
135 the most activity, but not significantly different from vancomycin alone. The addition of

136 heparin to the antibiotic lock solution did not have a significant effect on the activity of
137 either antibiotic against these strains.

138

139 **Drug stability.** Telavancin and vancomycin solutions were evaluated for concentration
140 at least in duplicate before and after incubation. Lock solutions increased in
141 concentration after 72h incubation (Table 1). We attempted measuring concentrations
142 of heparin-containing lock solutions after 72h incubation, however, the added heparin
143 interfered with interpretation of these results. (data not shown).

144 **DISCUSSION**

145 As large numbers of patients continue to be dialyzed through long-term intravascular
146 catheters and long-term intravascular catheter use continues to be important in caring
147 for many patients; a niche exists for the ideal antimicrobial agent to be used as an ALS
148 for catheter salvage. If successful, ALS use should reduce the cost and complications
149 of catheter removal and reinsertion.

150 In a previous study, telavancin prevented biofilm formation by biofilm-forming
151 staphylococci and enterococci at concentrations below the MIC.¹⁴ In the current study
152 testing eradication of formed biofilms, telavancin at concentrations 20,000-166,666x the
153 MIC and vancomycin at concentrations 2,500-5,000x the MIC (except for the VRE strain
154 which was ~20x the MIC) reduced the bacterial burden, but did not completely eradicate
155 these strains. While the concentrations of both vancomycin and telavancin increased
156 over the 72h period, we believe this was due to losses in volume from the lumen during
157 incubation.

158 The activity of vancomycin against vancomycin-resistant enterococci (VRE) may reflect
159 the high concentration used (~20x the MIC). Of note, the VRE strain produced less
160 biofilm than the other strains, making it less difficult to eradicate. We hypothesize that
161 the decreased activity of telavancin against *S. aureus* and *E. faecalis* may be partially
162 due to the presence of mannitol (125% w/w telavancin) in the drug formulation.²³
163 Mannitol is a sugar alcohol that can be fermented by *S. aureus* and some *Enterococcus*
164 strains, but not by *S. epidermidis*. Mannitol increases *S. aureus* biofilm formation,²⁴

165 which may lead to reduced ALS activity. The activity of the ALS tested against these
166 strains may be isolate-specific, likely reflecting the amount of biofilm produced.

167 Activity of the telavancin lock solutions may have been reduced by drug binding to the
168 catheter surface. Recent recommendations have suggested adding polysorbate 80 (P-
169 80) and dimethyl sulfoxide (DMSO) to telavancin for MIC testing to decrease binding to
170 the polystyrene surface resulting in a decreased MIC.²⁵ MICs were previously tested
171 without P-80 and DMSO and may appear falsely elevated compared to MICs with the
172 more recent method. Addition of P-80 and DMSO may increase activity of lock
173 solutions by decreasing binding to the polyurethane catheter; however, clinical utility is
174 limited unless a commercial product containing these additives is available.

175 Addition of benzyl alcohol-containing heparin to the antibiotic solution significantly
176 reduced antimicrobial activity of vancomycin against *S. epidermidis* and *E. faecalis*,
177 which we hypothesize may be due to stimulated biofilm growth. The influence of heparin
178 and benzyl alcohol on staphylococcal biofilm growth has been reported.²⁶⁻²⁹ Data on
179 the influence of heparin and benzyl alcohol on enterococcal biofilms are lacking. The
180 minimal activity for all locks containing heparin may demonstrate heparin-induced
181 biofilm growth in enterococci. We did not observe a reduction in antibiotic activity with
182 heparin against *S. aureus*, which may be concentration-dependent. A previous study by
183 our laboratory demonstrated significant reductions in activity of vancomycin 2mg/mL,
184 linezolid 1mg/mL and 2mg/mL in combination with heparin 5000 units/mL (benzyl
185 alcohol 0.45%). (unpublished data)

186 Normal saline demonstrated greater activity in our *in vitro* assay than expected. This is
187 likely due to disturbance of biofilm and removal of planktonic bacteria during lock
188 solution instillation and removal, which was not quantified. Normal saline has previously
189 demonstrated a reduction in formed biofilms of $\sim 1 \log_{10}$ CFU/mL over 24h.³⁰ Detachment
190 of some planktonic bacteria from the biofilm would be expected due to the lack of
191 nutrients in the lock solutions and a 72h incubation period. High antibiotic
192 concentrations or osmotic stress present in the ALS can stimulate biofilm formation,³¹
193 but as these are absent in saline solutions, detachment may be greater. Planktonic
194 bacteria that detached from the biofilm would either be removed during lock solution
195 withdrawal or potentially killed in an ALS; however these bacteria were not quantified in
196 our study. This exemplifies the clinical importance of lock withdrawal instead of flushing
197 lock solutions (and any planktonic bacteria within them) into the patient.

198 We hypothesize that the activity of normal saline is related to the amount of biofilm
199 produced by each strain tested, as demonstrated by saline having particularly more
200 activity than expected against the VRE strain that produced less biofilm. It is also
201 important to note, that activity of the solutions average $\sim 2-3 \log_{10}$ CFU/mL, even for the
202 antibiotic-containing lock solutions. This reduction from a baseline biofilm of 10^8
203 CFU/mL, left $\sim 10^5-10^6$ CFU/mL remaining in the catheter lumen. Activity may be
204 increased by repeated lock instillation and removal, as in clinical practice.

205 There are some limitations to this work. A small number of isolates were tested. There
206 are multiple possible explanations for the inability of the ALS tested to eradicate the
207 microbial load which was not explored further, such as additives inhibiting bactericidal
208 activity of antibiotics tested or stimulating biofilm formation. Increased biofilm formation

209 could also be interpreted as larger biomass growth, and/or stronger attachment, both of
210 which would result in more recovered cells at 72h.

211

212

213 **CONCLUSIONS**

214 Telavancin and vancomycin are active in reducing biofilm-forming staphylococci and
215 enterococci in a central venous catheter model, but were unable to completely eradicate
216 the biofilm-forming strains evaluated. Addition of preservative-containing heparin
217 sodium 2500 units/mL to vancomycin reduces activity against *S. epidermidis* and *E.*
218 *faecalis*. Finding the ideal ALS with antibiofilm activity and a minimal side-effect profile
219 remains of great interest to investigators and to the clinical community.

220

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228

229

230 **Conflict of Interest and Disclosures**

231 The views expressed are those of the authors and do not necessarily represent the
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241

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Figure 1. Log reduction (CFU/mL; mean \pm standard error of the mean) of an inoculated catheter containing biofilm-forming A) *Staphylococcus epidermidis*, B) *Enterococcus faecalis*, and C) *Staphylococcus aureus* locked for 72h with antibiotic, heparin, or normal saline.^c

A *S. epidermidis* (2 strains: ATCC35984 and clinical strain L369D; n=18)

B *E. faecalis* (2 strains: ATCC29212 and clinical strain L2022; n=18)

C *S. aureus* (4 strains: 2 MSSA: ATCC35556 and clinical strain L2, and 2 MRSA: clinical strains L32 and L83; n=36)

^c NS= normal saline

Hep = heparin sodium 2500units/mL with 0.45% benzyl alcohol

TLV = telavancin 5mg/mL

TLVH= telavancin 5mg/mL with heparin

VAN = vancomycin 5mg/mL

VANH= vancomycin 5mg/mL with heparin

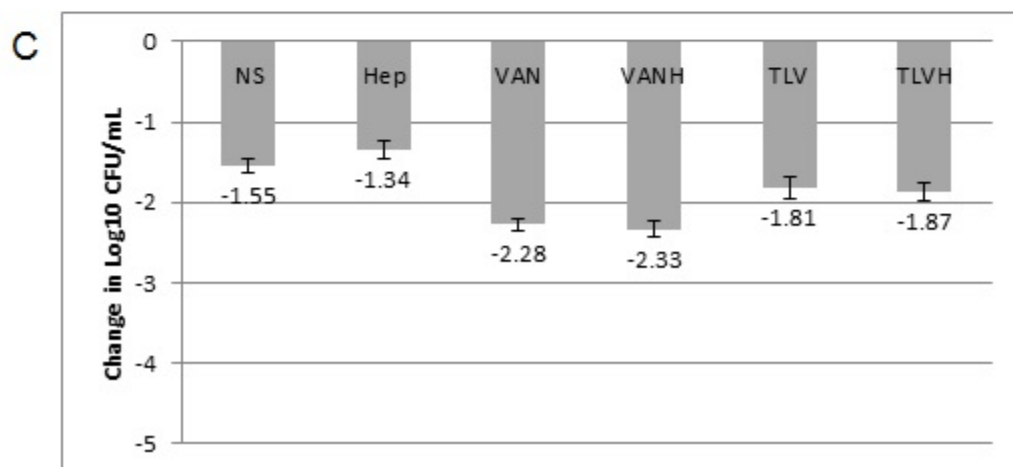
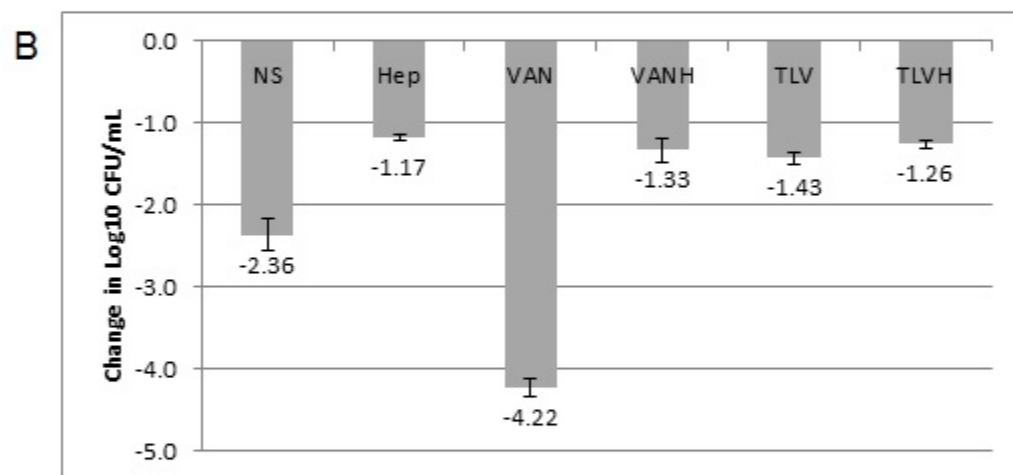
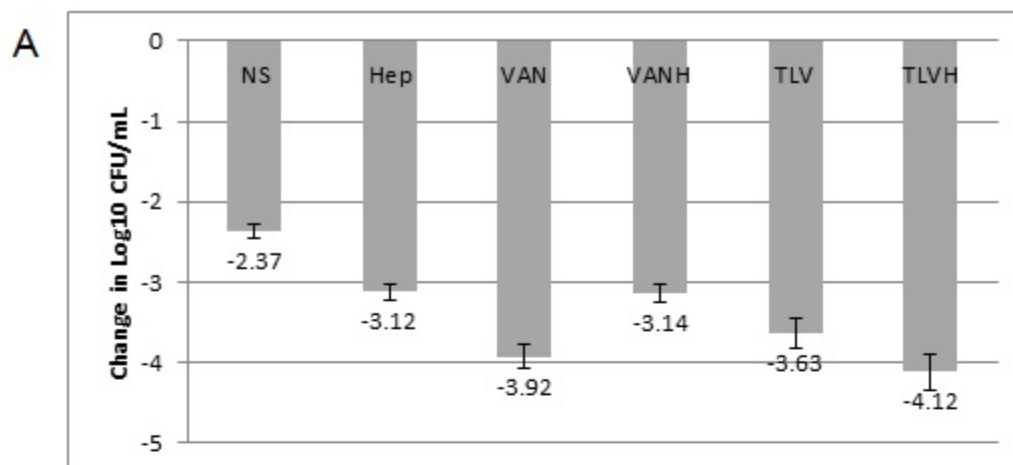


Table 1. Concentrations of antibiotic lock solution stock and after 72 hour incubation in a central venous catheter. Targeted concentrations were 5 mg/mL.

Antibiotic	Stock Concentration (mg/mL)	72 hour Incubation (mg/mL)
Telavancin	4.5 ± 0.8	4.9 ± 0.1
Vancomycin	5.0 ± 0.2	5.8 ± 0.02